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REMARKS

These remarks are in response to the Office Action mailed January 14, 2004. Claims 60, 74 and 76 have been canceled without prejudice to Applicants' right to prosecute the canceled subject matter in any divisional, continuation, continuation-in-part, or other application. Claims 41, 61, 66, 75 and 80-82 have been amended. Support for the amendments can be found, for example, in original claims 60, 74 and 76. No new matter is believed to have been introduced.

I. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 41-45, 49-51, 56, 58-61 and 63-82 stand rejected under 35 U.S.C. §112, first paragraph, because while the specification is enabling for a method for inhibiting uncontrolled proliferation of neoplastic cells in a subject, the method comprising administering at the neoplastic cells any of the claimed retroviral vectors as claimed in each of the presently pending base claims, and administering to said subject a prodrug which is activated by the expression of a suicide gene, with the provision that the claimed heterologous nucleic acid encodes the suicide gene; the specification allegedly does not enable one of skill in the art to make or use the invention

commensurate in scope with these claims. Applicants respectfully traverse this rejection.

A significant portion of the grounds for the rejection of the claims under 35 U.S.C. §112, first paragraph, is based on the alleged unpredictability of the art of gene therapy in general. The issue of whether the specific instant claims are enabled by the specification should not turn on the state of the art of gene therapy as generally discussed throughout the Office Action. Instead, the relevant question with regard to enablement of the subject matter of the instant claims is whether the particular steps and materials of the claimed methods are described in the specification in such a way as to enable one skilled in the art to make and use the subject matter as claimed.

The Examiner points to a number of references including Anderson and Vile et al. as an assessment of the state of the art of gene therapy at the time the instant invention was made, citing problems of impracticality and unpredictability that include issues associated with (i) poor delivery systems; (ii) poor gene expression after delivery; and (iii) one animal model is not predictive of others (see page 5 of the Office Action; citing to Anderson).

It is respectfully submitted that such a selective reading of Anderson, in which statements regarding the state of gene therapy in 1997 and 1998 are taken out of context, has resulted in a mischaracterization of the reference that cannot validly be relied on to support an allegation of unpredictability of gene therapy. For example, Anderson also points out that there are a number of clinical trials and a large number of patients that have been treated using gene therapy techniques in 1998. Although Anderson suggests that gene transfer is not an established clinical treatment regime, it clearly had been demonstrated, based on actual clinical trial data that therapeutically relevant genes could be transferred into human patients and be expressed within the patient in such a manner as to show biologic efficacy.

Applicant is not aware of any requirement under current U.S. patent law specifying particular minimum levels of optimization and certified efficacy in order for a treatment-related area of art to qualify as sufficiently "predictable" such that lack of enablement under 35 U.S.C. §112, first paragraph, is not a consideration.

The relevant standard is not that of an established, fully optimized, clinical course of treatment; rather, even in an

unpredictable art, a patent application satisfies the requirements of 35 U.S.C. §112, first paragraph, so long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the claimed subject matter with reasonable, but not undue, experimentation. There is no requirement that a treatment method achieve a specified level of efficacy or efficiency in order to be considered "enabled" by the specification.

It appears that the Examiner, in asserting the unpredictability of the art of gene therapy, has equated "limitations" in the art in 1997 with "unpredictability." It is respectfully submitted that although methods of gene therapy may be associated with certain limitations and limited success, this does not establish the art as unpredictable. In fact, with respect to methods of gene therapy, the well-studied, -identified and -characterized limitations of the art, as determined through years of research and, several clinical trials, make the methods all the more predictable. The practitioner is well aware of the potential obstacles and clearly knows what he or she is up against in designing and carrying out such therapeutic methods. As such, it is

respectfully submitted, that although the art of gene therapy may not have been a routine, clinical practice at the effective filing date of the subject application, it was not so unpredictable as to qualify as a major factor in the determination of whether the requirements of 35 U.S.C. §112, first paragraph, are satisfied with respect to the instantly claimed subject matter.

Applicants respectfully submit that the originally filed application provides ample support for the scope of the pending claims. The methods of the invention are based on Applicants' discovery that novel replication competent retroviral vectors can be used to enhance the efficiency of transduction *in vivo*. The novel vectors utilize a cassette comprising an internal ribosome entry site (IRES) operably linked to a heterologous nucleic acid sequence encoding a polypeptide that converts a nontoxic prodrug to a toxic drug (i.e., a suicide gene). The cassette is positioned 3' to the sequence encoding the retroviral envelope and 5' to the 3' LTR sequence of the retroviral genome. Example 1 describes the construction of the vector and the insertion of the IRES-transgene into a position in the viral genome that enhanced the stability of the insert while linking expression of the inserted transgene to viral

coding sequences (see page 53, Example 1; see also page 54, lines 12-17). The IRES sequence was inserted just downstream from the envelope message but upstream from the 3' LTR (see Figure 2). The specification describes how the novel vector is capable of retaining and delivering a transgene encoding green fluorescence protein (GFP) to practically all cells in culture even with low initial transduction levels. Furthermore, the specification describes the replacement of the GFP transgene with a sequence encoding a polypeptide that converts a pro-drug in to a toxic drug, such as the Herpes simplex virus thymidine kinase (HSV-tk) gene and the E. coli purine nucleotide phosphorylase (PNP) gene (see, e.g., the specification at Example 8; and the attached Declaration by Dr. Noriyuki Kasahara).

A declaration by Dr. Noriyuki Kasahara under 37 C.F.R. §1.132 accompanies the present response. The declaration describes the manner in which one skilled in the art of gene therapy can use the method of the invention, in conjunction with the disclosed vectors, to treat a cell proliferative disorder. Specifically, the declaration provides data that clearly indicates the claimed methods can be used to treat a cell proliferative disorder (e.g. glioblastoma). The vector used in

the treatment comprise the vectors of the invention wherein the heterologous nucleic acid is a suicide gene. The declaration provides data that indicates that a therapeutic effect can be achieved by the methods and vectors described in the specification; i.e., that delivery of a heterologous nucleic acid sequence encoding a polypeptide that converts a nontoxic prodrug to a toxic drug to neoplastic cells in a subject provides a therapeutic effect.

Applicants further note that the data provided in the accompanying declaration utilize nude mice as a model for human neoplastic disorders. The use of immunocompromised animal models were useful for at least two reasons. First, Applicants utilized human neoplastic tissue implanted in animal models to provide support for the therapeutic benefit of the present invention to human cell proliferation disorders. The human neoplastic xenografts implanted in the immunocompromised animals would have been immediately rejected if implanted in immunocompetent animals, rendering the experimental model for identifying transduction and horizontal infection by RCR viruses in a human tumor model entirely useless. Second, even if a mouse tumor, as opposed to a human tumor, were induced to form in an immunocompetent mouse, an immune response mounted by such

an animal against an RCR virus of the invention may have the secondary effect of provoking an immune response against the tumor. Again, any results derived from this experiment could be interpreted as simply an activation of the host immune system by the introduction of RCR virus. Such results would be marginal or may be uninterpretable with regard to RCR viral transduction. Applicants submit that, absent the use of a human tumor in a human model, the best available animal model was used to generate a working example correlative to human RCR viral therapy.

Applicants further submit that the Training Materials for Examining Patent applications, with respect to enablement for chemical-biotechnical applications, has addressed the use of experimental animal models and concluded that "an *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" because that example "correlates" with a disclosed or claimed method invention." The Training Materials further state that "the evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." In addition, the courts have weighed-in on the issue, concluding that a rigorous or an invariable exact

correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

... based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence.

The Office Action appears to take the position that the art of gene therapy for treating cell proliferative disorders is highly unpredictable. In support of this, the Office Action cites to various publications and reports that allegedly describes the state of the art of gene therapy at the time the present application was filed. In contrast to the references cited by the Office Action, reports drafted in the same, or nearly the same, time period indicate that:

Enough information has been gained from clinical trials to allow the conclusion that human gene transfer is feasible, can evoke biologic responses that are relevant to human disease, and can provide important insights into human biology...accomplishments to date are impressive, and the logic of the potential usefulness of this clinical paradigm continues to be compelling.

(See Crystal, Science, 270:404, 1995).

For example, Applicants point to a publication that states that gene therapy was used to treat malignant brain tumors (see Ram et al., "Therapy of malignant brain tumors by intratumoral

implantation of retroviral vector-producing cells," Nat Med, 3:1354-61, 1997). This publication provides evidence that intratumoral implantation of murine cells modified to produce retroviral vectors containing the herpes simplex virus-thymidine kinase (HSV-TK) gene induces regression of experimental brain tumors in rodents after ganciclovir (GCV) administration.

Further, the Office Action cites to Anderson (Nature) and Miller et al. (Human Gene Therapy) as supporting the concept that transduction efficiencies are notoriously inadequate for vectors used in gene therapy methods. Applicants note that the vectors used in the presently claimed methods address precisely these issues. The present vector is "replication competent" and achieves transduction and expression efficiencies never achieved by previous vectors (see e.g., Example 9 of the specification). Consequently, Applicants submit that statements contained in the Office Action regarding the "shortcomings" of current gene therapy methods may be accurate for those methods utilizing non-replication competent vectors, but are not accurate for methods employing the RCR vectors disclosed in the present application.

Applicants submit that one of skill in the art could readily identify, without undue experimentation, additional heterologous nucleic acid sequences for introduction into a

replication competent recombinant retroviral (RCR) vector of the invention, as well as routes of administration and therapeutic dosages that would be applicable in the method of the present invention. With regard to dosage, §608.01(p) of the MPEP states that, "It is not necessary to specify the dosage or method of use if it is obvious to one skilled in the art that such information could be obtained without undue experimentation." The law therefore does not require recitation in a therapeutic method claim of how a vector (or genetically modified cell) is to be administered when a person of ordinary skill in the art could determine the most proper administration route without undue experimentation. Nevertheless, Example 8 and Example 9 of the present specification provide examples of transduction and intratumoral spreading of the viral vector, including routes of administration and multiplicity of infection (MOI) calculations. Applicants note that the invention is the first to provide an RCR vector capable of "horizontal" infection through a targeted tissue for delivery of a therapeutic agent. One of skill in the art can easily determine the amount of vector necessary to elicit a therapeutically-effective response given that even a minimal amount of the vector will be sufficient to allow for horizontal infection of specifically targeted cells.

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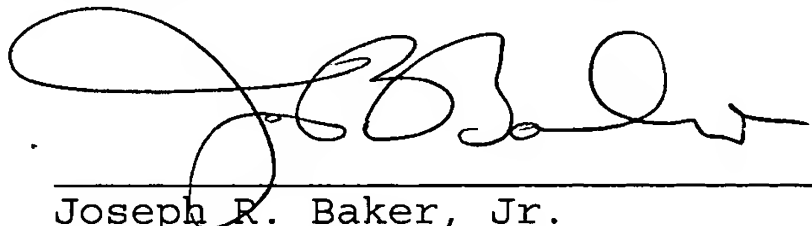
Applicants submit that, in light of the information contained in the present specification and in view of the level of skill in the art of gene therapy, it would not require undue experimentation to practice the invention. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph, be withdrawn.

Enclosed is a \$475 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: _____

7/13/04



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Noriyuki Kasahara et al. Art Unit : 1632
Serial No. : 10/045,178 Examiner : Dave Trong Nguyen
Filed : January 11, 2002
Title : GENE DELIVERY SYSTEM AND METHODS OF USE

DECLARATION OF NORIYUKI KASAHARA
UNDER 37 C.F.R. §1.132

Dear Sir:

1. I, Noriyuki Kasahara, declare and say I am a resident of Los Angeles, California. My residence address is 8446 Kirkwood Drive, Los Angeles, California 90046.

2. I, Noriyuki Kasahara, hold a Bachelor degree in Medical Science that I received from Tokyo Medical and Dental University, in 1986. I further hold an M.D. degree that I received from Tokyo Medical and Dental University in 1993, and a Ph.D. degree that I received from the University of California, San Francisco (UCSF) in 1994. I received Board certification in the field of Clinical Pathology from the American Board of Pathology in 1996. I am currently an Associate Professor in the Department of Medicine at the University of California, Los Angeles (UCLA) David Geffen School of Medicine, 675 Charles E. Young Drive South, MRL-1551, Los Angeles, CA. I am an expert in

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I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

July 13, 2004

Date of Deposit

Signature

Teri Barnett

Typed or Printed Name of Person Signing Certificate

the fields of clinical pathology, molecular biology, virology, virus-based gene delivery vector technology development, and gene therapy. I am also a member of the Scientific Committee on Viral Gene Transfer Vectors of the American Society of Gene Therapy, a member of the Executive Council of the International Society of Cancer Gene Therapy, and on the editorial board of *Cancer Gene Therapy*.

3. I am an inventor of the claims of the above-identified patent application. I directed others and personally performed the research leading to the invention disclosed and claimed therein.

4. I have read the Office Action dated January 14, 2004, issued for the above-identified application. I understand that the Examiner has rejected the pending claims on the grounds that the specification allegedly fails to provide an enabling disclosure for methods of treating a mammal having a cell proliferative disorder with a replication competent retrovirus. The Examiner alleges that the art of gene therapy is unpredictable and poorly developed.

5. The specification of the above-referenced patent application describes replication-competent retrovirus (RCR) vectors. These vectors are unique, in part, because their design greatly enhances genetic and functional stability of the vector. All previously reported replication-competent vectors have contained transgene insertions within the 3' long terminal repeat (LTR) which were invariably deleted within 1 or 2 serial

passages. To alleviate this problem, we inserted an internal ribosome entry site (IRES) sequence and multiple cloning site into a less sensitive position in the viral genome that linked transgene expression to viral coding sequences. The IRES-multiple cloning sequence is positioned between the env termination codon and a polypurine-rich tract within the 3' untranslated region (UTR) that binds reverse transcriptase. The cloning site is useful for insertion of transgene coding sequences, including marker genes such as green fluorescent protein (GFP), suicide genes such as yeast cytosine deaminase (CD) or purine nucleoside phosphorylase (PNP), and expression of each of these transgenes is linked to viral gene expression through the IRES sequence. There have been no previous reports regarding use of an IRES sequence to link transgene expression with viral gene expression in modified/engineered replication-competent retrovirus vectors; hence this represents a novel design strategy.

6. In order to expand the infectivity of the glZD-GFP vector (described throughout the specification, e.g., FIG. 1B and page 53, line 19 to page 54, line 11) to include human cells, we replaced the envelope of the vector, using overlap-extension PCR with the amphotropic envelope of the 4070A murine leukemia virus, generating the plasmid pACE-GFP, shown in Appendix B (attached hereto). The 4070A sequence was obtained from plasmid pHIT60.

These RCR vectors achieve efficient transgene delivery to solid tumors in vivo. U-87 human glioma cells (5×10^5 cells) were first implanted subcutaneous into athymic nu/nu mice.

Tumors were allowed to grow up to 0.5 cm in diameter, then PBS vehicle control, the amphotropic RCR vector ACE-GFP (1.2×10^5 TU/100 μ l), or a conventional replication-defective retrovirus vector expressing GFP (1.0×10^5 TU/100 μ l) was injected into the tumor. After sacrifice at serial time intervals 2, 4, and 6 weeks after vector inoculation, quantitation of GFP expression in the transduced tumors was performed by FACS analysis immediately after dissection and collagenase digestion to obtain a single-cell suspension of the tumor sample.

FACS analysis of replication-defective vs. RCR vector-transduced subcutaneous gliomas is provided in Figure 1, below. The percentage of GFP positive cells in the freshly dissected tumors that had been infected by the replication-defective vector was low, only 1.2% at 2 weeks, and 0.2% at 6 weeks post-vector injection (Figure 1, B-C), consistent with the results observed in clinical trials. In contrast, the percentage of GFP positive cells infected by the replication-competent retrovirus (ACE-GFP) was 70.6%, 90.2%, and 97.2% at 2, 4, and 6 weeks post-injection, respectively (Figure 1, D-F).

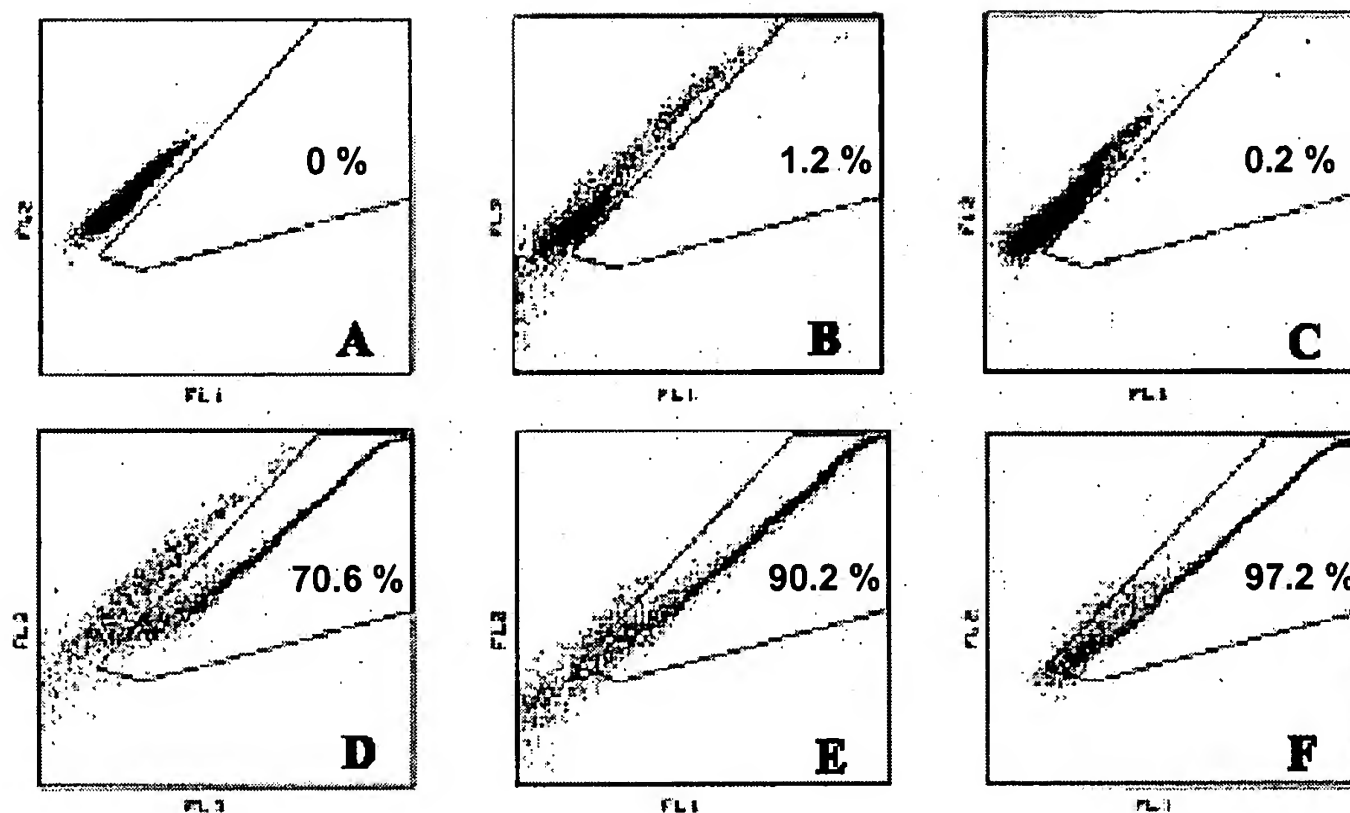


FIGURE 1

These results demonstrate that, in contrast to conventional replication-defective vectors, the RCR vector was capable of essentially complete transduction of the entire U-87 tumor mass within 6 weeks.

7. To examine the suicide gene function of RCR vector ACE-CD, which was engineered to carry the CD gene (Fig. 2a), fully transduced U-87 cells were treated with 5-FC at various concentrations ranging from 0.1 to 5 mM. To detect any potential non-specific toxicity due to the prodrug itself, uninfected and ACE-GFP transduced control cells were also treated with corresponding concentrations of 5-FC. The 5-FC prodrug alone showed no cytotoxicity at concentrations of 2 mM or less on uninfected cells or ACE-GFP transduced cells. ACE-CD

infection resulted in potent cell killing with 5-FC at all concentrations used, and killing efficiency was well correlated with increasing 5-FC dosage (Fig. 2b).

ACE-CD transduced U-87 cells mixed with uninfected cells at varying percentages were treated with or without 5-FC, and cell viability over time was normalized to that of a negative control composed of uninfected cells without prodrug (0% /5-FC-) (Fig. 2c). The 5-FC prodrug alone at 2 mM concentration (0% /5-FC+) and the ACE-CD virus alone without addition of prodrug (100% /5-FC-) were both confirmed to be nontoxic. However, when initially even as few as 0.1% of the tumor cells were producing ACE-CD, substantial cell killing was observed over time after incubation with 5-FC (Fig. 2c); this killing effect could not have been achieved by a bystander effect alone, and indicates amplification of the transduced population by replicative spread of the vector. Higher percentages of initially transduced cells in the culture plates achieved correspondingly faster clearance of the tumor cell population, and correlated with the kinetics of viral replication observed previously.

Figure 2

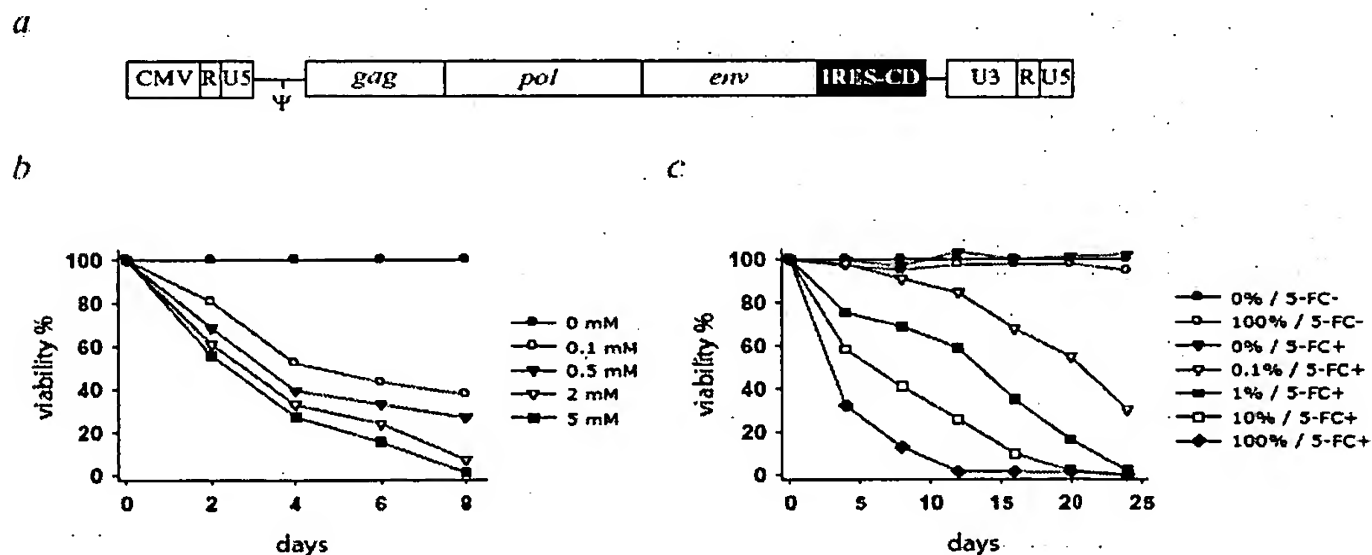
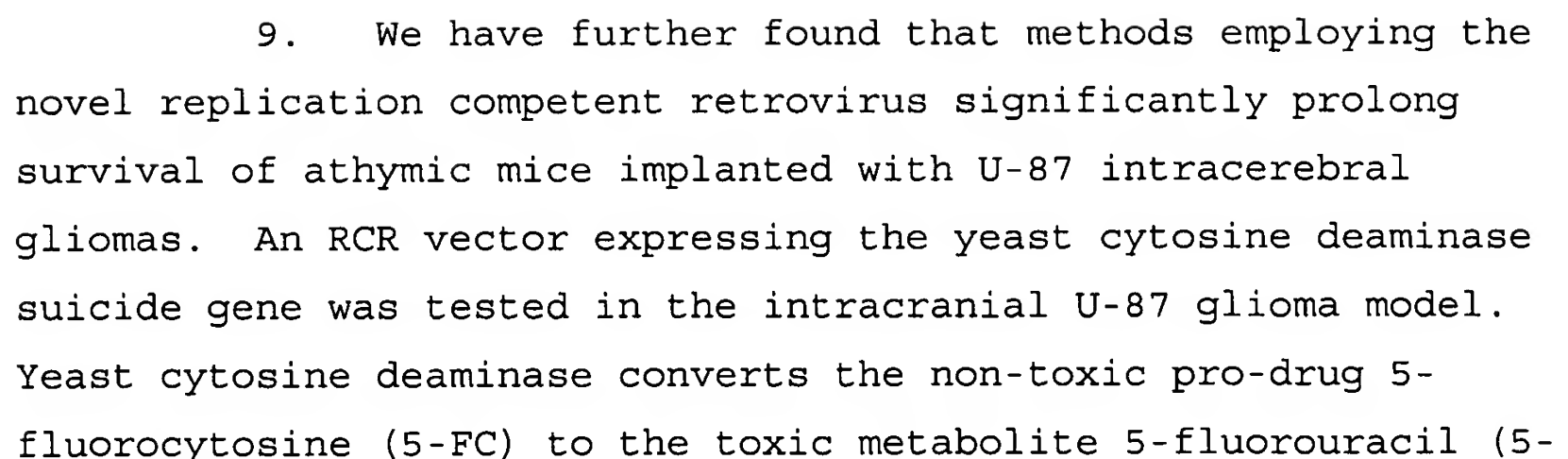


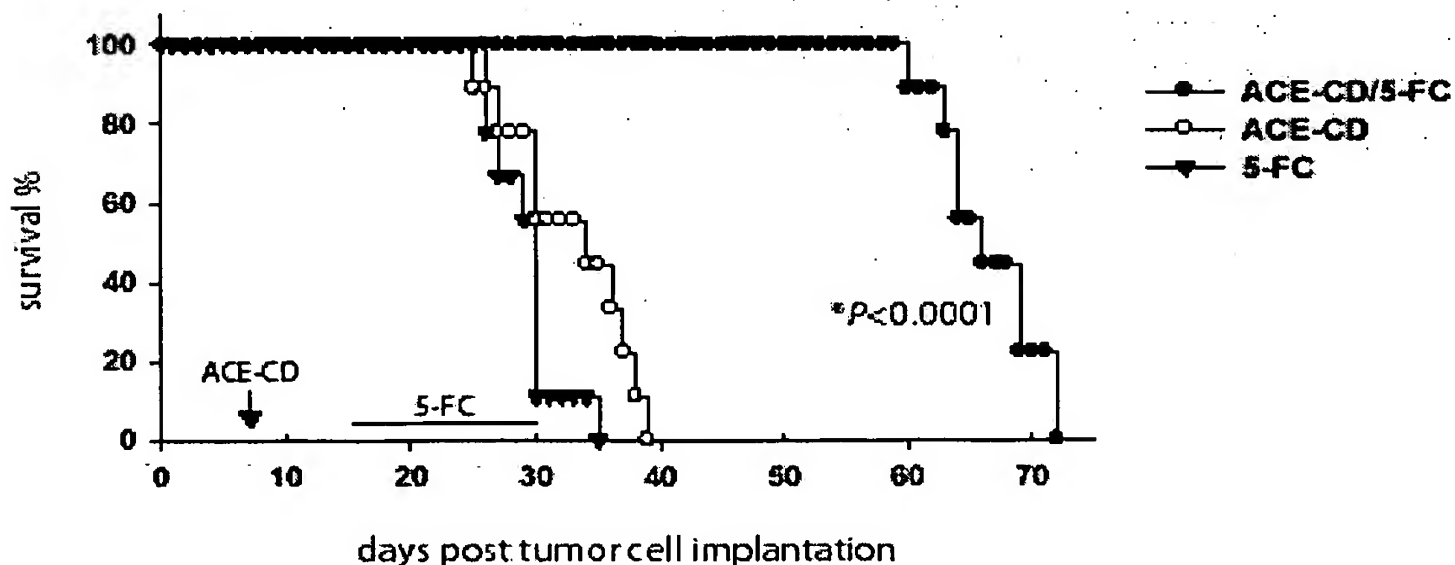
Figure 3



As part of a strategy for the specific killing of tumor cells using the replicating vector, the GFP marker gene of pACE-GFP was replaced with a "suicide" gene encoding cytosine deaminase (CD) (see, e.g., Fig. 2A, above). The resulting vectors were termed pACE-CD.

One week after tumor implantation, approximately 1.0×10^4 TU in a total volume of $10 \mu\text{l}$ was stereotactically injected into intracranial U-87 tumors in 2 groups of mice ($n = 9$ each). An additional group ($n = 9$) received only PBS vehicle control. Eight days after vector transduction, the 5-FC prodrug, 500 mg/kg/day , was given for 15 consecutive days by daily intraperitoneal injection to one of the ACE-CD injected groups and to the PBS vehicle injected group. The remaining ACE-CD injected group received only daily intraperitoneal injections of PBS for 15 consecutive days. The mice treated with ACE-CD plus a single cycle of 5-FC prodrug showed a doubling of median survival over a follow-up period of more than 70 days (See Figure 4), compared to mice treated with either ACE-CD/PBS ($p < 0.0001$) or PBS/5-FC prodrug ($p < 0.0001$).

Figure 4



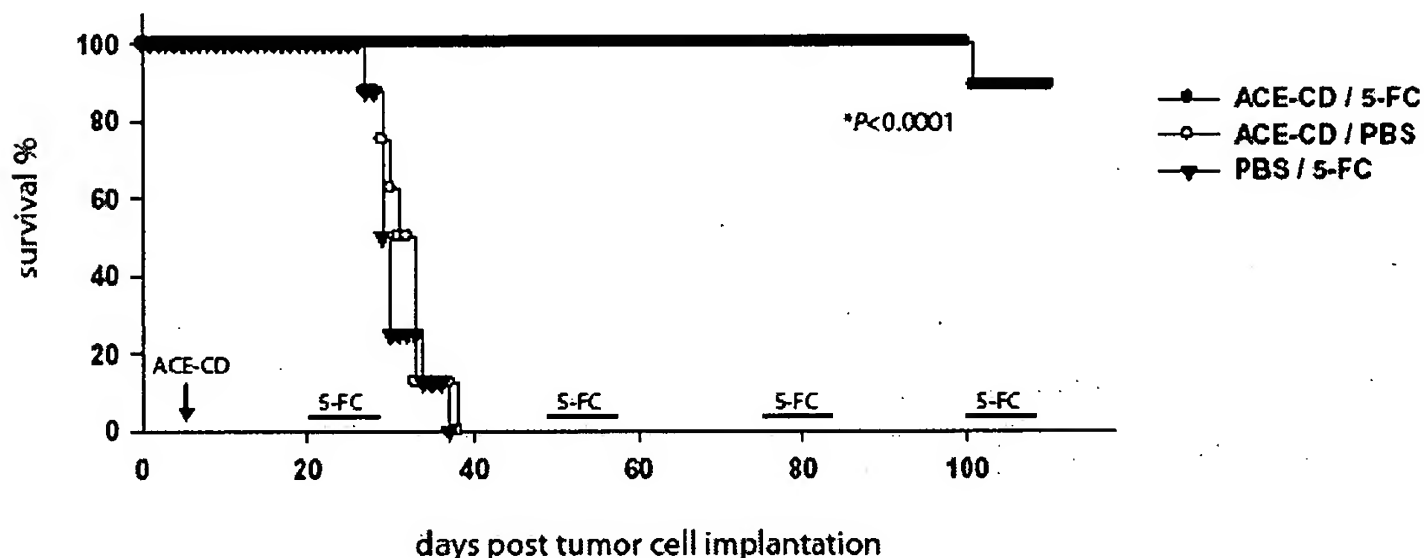
10. A single intratumoral injection of ACE-CD vector or saline vehicle was performed after prior establishment of intracerebral U-87 gliomas; subsequently, multiple cycles of 5-FC prodrug or saline vehicle administration were performed by intraperitoneal injection for 8 consecutive days at 3 week intervals. Both control groups (Fig. 5a, ACE-CD/PBS, PBS/5-FC) showed similar results with a median survival time of approximately 30 days, and none of the mice in any control group survived longer than 38 days. In contrast, the group treated with ACE-CD plus multiple cycles of 5-FC showed 100% survival for more than 100 days, i.e., more than triple the median survival time of the control groups (Fig. 4a; $P < 0.0001$). Interestingly, toward the end of each 3 week rest interval during which prodrug administration was interrupted, it was observed that the animals repeatedly became moribund and exhibited reduced mobility and poor feeding and grooming; strikingly, however, with commencement of the next cycle of 5-FC administration, the animals regained normal mobility and feeding behavior, suggesting that significant suppression of tumor regrowth associated with symptomatic relief was achieved in each cycle.

Histological examination again revealed that control groups already showed extensive growth of multiple large tumors throughout the CNS (Fig. 5b, PBS/5-FC) by the time of death <38 days post-tumor cell implantation. Immunohistochemistry using a viral envelope-specific antibody again confirmed that, within this time frame, the RCR vector achieved highly efficient spread within every observable glioma lesion throughout the CNS; this

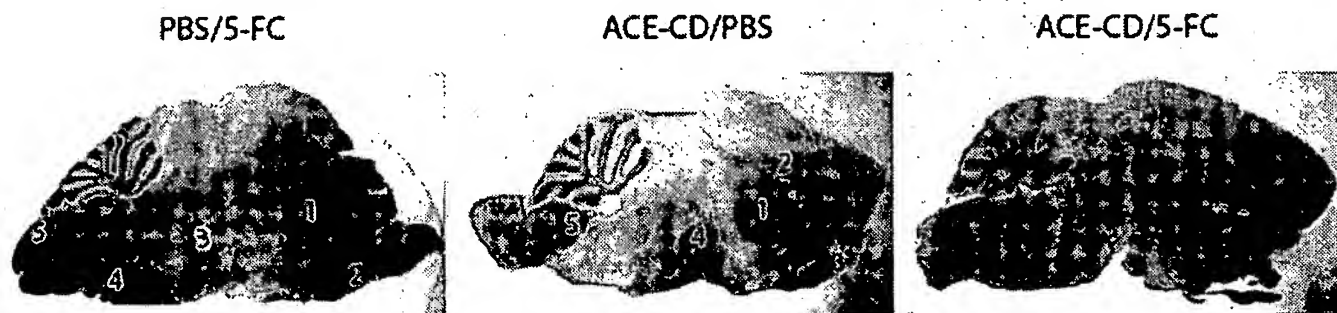
replication was again observed to be highly restricted to the tumor foci without significant spread to adjacent normal brain (Fig. 5b, ACE-CD/PBS). In contrast, in the group receiving ACE-CD followed by multiple cycles of 5-FC administration, at the time of termination >100 days post-tumor implantation the majority of animals showed no evidence of significant ectopic foci apart from the primary inoculation site, which again showed profound inhibition of tumor growth (Fig. 5b, ACE-CD/5-FC).

Figure 5

a



b



11. The biodistribution of ACE-CD was analyzed by PCR of genomic DNA from various extratumoral organs using primers specific for the CD sequence. The RCR sequence could be readily detected in the transduced glioma tissue, but extratumoral spread of RCR vector was not detected in any of the normal tissues examined, including liver, lung, spleen, bone marrow, GI tract, kidney, skin, and contralateral normal brain (Fig. 6). Biodistribution of ACE-CD during prolonged replication in vivo. Genomic DNA isolated from intracranial tumor as well as various extratumoral tissues from the same ACE-CD-injected animal was analyzed by PCR using primer flanking the CD transgene. The expected size of the full-length PCR product is 458 bp. A 525-bp fragment of the β -casein gene was also amplified from same genomic DNA sample as an internal control for the PCR procedure. M: 100-bp DNA marker. 1: lung. 2: liver. 3: esophagus and stomach. 4: intestine. 5: spleen. 6: kidney. 7: skin. 8: bone marrow. 9: contralateral brain (normal). 10: intracranial tumor. 11: negative control tumor (no virus injection).

Figure 6



12. The specification of the above-referenced patent application provides ample guidance to the person of ordinary skill in the art to successfully practice the claimed invention. For example, one skilled in the art at the time the application was filed would know, given the information provided in the specification, that treatment of a subject with an RCR vector of the invention would likely result in a therapeutic effect.

13. All of the experiments described in the specification, in conjunction with above experiments which were performed according to methods and the examples described in the specification, demonstrate that the claimed invention is useful for efficiently transferring a therapeutic polypeptide to a large number of neoplastic cells in vivo. The experiments further indicate that, post-infection, the RCR vector produces therapeutic levels of a pro-drug in a subject. Using the methods and compositions described in the specification, one of ordinary skill in the art would have a reasonable expectation that the claimed invention would be applicable to providing a expression of a pro-drug in neoplastic cells for the purpose of treating a cell-proliferative disorder in a subject in need of such treatment.

14. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the

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United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

A handwritten signature in black ink, appearing to read "N. Kasahara", written in a cursive style.

Date: July 12, 2004

Noriyuki Kasahara, M.D., Ph.D.

EXHIBIT B

